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Plasma Cell Leukemia Evolving Into Aggressive Extramedullary Plasmacytoma by Clonal Selection

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INTRODUCTION

Plasma cell leukemia (PCL) is a rare form of plasma cell dyscrasia characterised by circulating plasma cells, diffuse disease infiltration of the marrow, a high tumor load, an aggressive clinical course, and a poor survival [1]. We report the histologic and molecular features of a unique case of de novo PCL that showed an evolution into an anaplastic plasmacytoma.

MATERIALS AND METHODS

A 55-year-old man was referred for investigation of anemia. A full blood count showed hemoglobin: 8.0 g/dl, white cell count: 22.5×10^9/L (70% circulating plasma cells), and platelet count: 10×10^9/L. Ultrasonogram of the abdomen was normal. A monoclonal immunoglobulin G (IgG) of 4,546 mg/dl (70–1,850 mg/dL) was present with immunoparesis. A bone marrow biopsy showed 80% abnormal plasma cells, confirming the diagnosis of de novo PCL. He was given chemotherapy (VAD) consisting of intravenous vincristine (0.4 mg/day × 4), adriamycin (14 mg/day × 4), and dexamethasone (40 mg/day × 12), which resulted in the disappearance of circulating plasma cells and a fall in IgG level to 2,588 mmol/dL. However, a massive pelvic tumor was demonstrated by computerised tomography (CT) scan 1 month afterwards. A second course of VAD was administered together with bolus intravenous injections of cyclophosphamide (600 mg × 4), resulting in a major resolution of the pelvic mass as shown by CT scanning. A third course of chemotherapy was given, but a later CT scan showed disease progression that became refractory to treatment. The patient died 3 months afterwards.

RESULTS AND DISCUSSION

The H & E stained sections of the pelvic tumor revealed a pleomorphic infiltrate composed of small and medium cells with plasmacytic differentiation, and bizarre large multinucleated anaplastic cells with prominent nucleoli (Fig. 1a). Immunohistochemical stains showed that an occasional large cell was positive for EMA and occasional cells showed cytoplasmic staining for CD3. Light chain restriction was equivocal. The overall findings were in keeping with an anaplastic transformation of an underlying plasma cell dyscrasia. To confirm the plasma cell nature of the pelvic tumor, Southern analysis with an immunoglobulin gene J_H probe was performed after restriction enzyme digestion of DNA with *Bam*HI and *Hind*III. For the *Bam*HI DNA digest, a single rearrangement band was found in both the marrow and the pelvic tumor (Fig. 1b). On the other hand, in the *Hind*III DNA digest, two rearrangement bands were observed in the marrow specimen. This might be due to one of two possibilities: biallelic immunoglobulin gene rearrangements or gene rearrangements from two different clones. Interestingly, only one of the two rearrangement bands was observed in the pelvic tumor. As histologically very little normal tissue was observed in the pelvic tumor, the presence of a strong germline band excluded the possibility that the pelvic tumor clone was derived from deletion of one of the alleles of a marrow clone with biallelic rearrangements. Therefore, it is most likely that the two rearrangement bands observed in the marrow DNA were derived from two different clones, and that the pelvic tumor had arisen from one of the clones through selection. The single band in the *Bam*HI digest would be explained by one of the clones having a rearrangement not detected by this restriction enzyme digestion.

This case is unique in presenting with extramedullary

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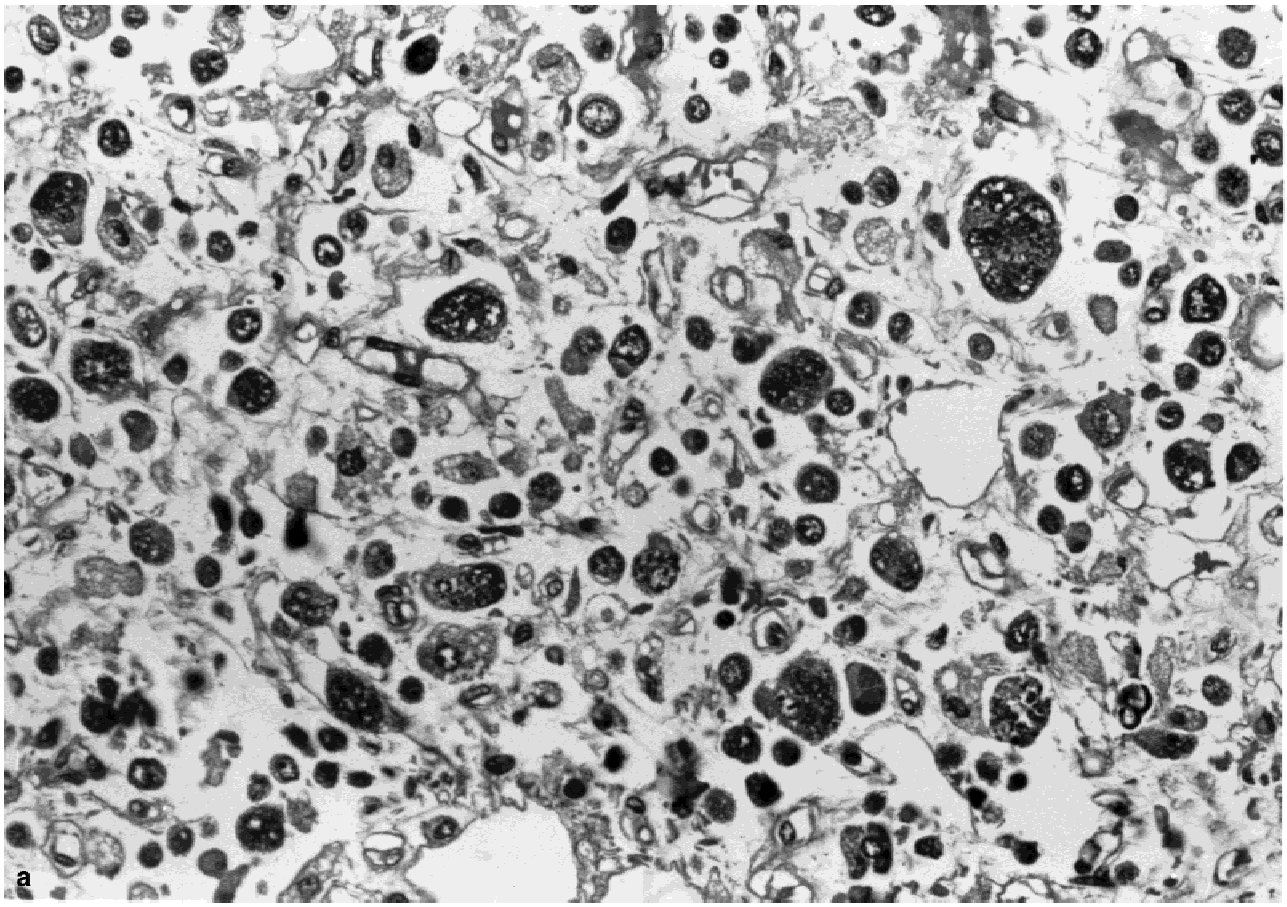

Fig. 1. a: Anaplastic plasmacytoma showing a pleomorphic infiltrate, with some small cells showing plasmacytic differentiation, and numerous bizarre multinucleated tumor cells that did not show any evidence of differentiation (hematoxylin and eosin staining, original magnification × 1,000). b: Southern blot of DNA from a normal control (N), marrow (M), and plasmacytoma (P) of the patient, hybridized with an immunoglobulin gene J_H probe. In the *Bam*HI digest, in addition to a germline band of 17 kb, a rearranged band of 24 kb is seen in both the marrow and the plasmacytoma, although the rearranged band was weaker in the latter. In the *Hind*III digest, in addition to a germline band of 9.9 kb, two rearranged bands of 9.3 and 4.6 kb are seen in the marrow. However, only one rearranged band of 4.6 kb is observed in the plasmacytoma.

plasmacytoma as a primary complication of PCL [2,3]. The other interesting finding was the rapid clinical progression to a tumor with very anaplastic cells bearing little resemblance to the usual histologic appearance of plasmacytomas. Indeed, the diagnosis of an anaplastic variant of plasmacytoma was made possible by the antecedent history of PCL and the subsequent demonstration of clonal rearrangement of the immunoglobulin gene.

Finally, another unusual feature is the apparent predominance in the plasmacytoma of one of the two subclones that constituted the PCL. It is now recognised that most plasma cell dyscrasias develop from a heavy chain isotype pre-switch circulating B cell [4,5] that undergoes further tumorigenic changes and clonal selection before and after isotype switching to produce an eventual dominant clone. Despite the monoclonality at the immunoglobulin level, a heterogeneity of subclones is demonstrable at the cellular level, all producing the same idiotype-specific antibodies [5]. Our case illustrates how this clonal selection process might have finally led to the predominance of an anaplastic clone that was refractory to treatment.

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